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10400

<110> MEDICO, Ed
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<120> RECOMBINANT PROTEINS DERIVED FROM HGF AND MSP

<130> 0471-0162P

<140> US 09/600,991

<141> 2000-09-15

<160> 22

<170> PatentIn version 3.1

<210> 1

<211> 1725

<212> DNA

<213> Artificial Sequence

<220>

<223> Magic F-1 DNA coding sequence

<400> 1

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| ctgctcccca | tcgccatccc | ctatgcagag | ggacaaagga | aaagaagaaa | tacaattcat | 120 |
| gaattcaaaa | aatcagcaaa | gactacccta | atcaaaatag | atccagcact | gaagataaaa | 180 |
| acaaaaaaag | tgaatactgc | agaccaatgt | gctaatagat | gtactaggaa | taaaggactt | 240 |
| ccattcactt | gcaaggcttt | tgtttttgat | aaagcaagaa | aacaatgcct | ctggttcccc | 300 |
| ttcaatagca | tgtcaagtgg | agtgaaaaaa | gaatttggcc | atgaatttga | cctctatgaa | 360 |
| aacaaagact | acattagaaa | ctgcatcatt | ggtaaaggac | gcagctacaa | gggaacagta | 420 |
| tctatcacta | agagtggcat | caaatgtcag | ccctggagtt | ccatgatacc | acacgaacac | 480 |
| agctatcggg | gtaaagacct | acaggaaaac | tactgtcgaa | atcctcgagg | ggaagaaggg | 540 |
| ggaccctggt | gtttcacaag | caatccagag | gtacgctacg | aagtctgtga | cattcctcag | 600 |
| tgttcagaag | ttgaatgcat | gacctgcaat | ggggagagtt | atcgaggctc | catggatcat | 660 |
| acagaatcag | gcaagatttg | tcagcgctgg | gatcatcaga | caccacaccg | gcacaaattc | 720 |
| ttgcctgaaa | gatatcccga | caagggcttt | gatgataatt | attgccgcaa | tcccgatggc | 780 |
| cagccgaggg | ctgggtgcta | tactcttgac | cctcacaccc | gctgggagta | ctgtgcaatt | 840 |
| aaaacatgcg | ctgacaaaagc | ttcgggcggt | ggcgggtctg | gtggcggtgg | ctccggcggt | 900 |
| ggcgggttctc | tagaggggaca | aaggaaaaga | agaaatacaa | ttcatgaatt | caaaaaatca | 960 |
| gcaaagacta | ccctaatacaa | aatagatcca | gcactgaaga | taaaaaccaa | aaaagtgaat | 1020 |
| actgcagacc | aatgtgctaa | tagatgtact | aggaataaag | gacttccatt | cacttgcaag | 1080 |
| gcttttgttt | ttgataaagc | aagaaaacaa | tgctctggt | tccccttcaa | tagcatgtca | 1140 |
| agtggagtga | aaaaagaatt | tggccatgaa | tttgacctct | atgaaaacaa | agactacatt | 1200 |
| agaaactgca | tcattggtaa | aggacgcagc | tacaaggga | cagtatctat | cactaagagt | 1260 |
| ggcatcaaat | gtcagccctg | gagttccatg | ataccacacg | aacacagcta | tcggggtaaa | 1320 |
| gacctacagg | aaaactactg | tcgaaatcct | cgaggggaag | aagggggacc | ctggtgtttc | 1380 |
| acaagcaatc | cagaggtacg | ctacgaagtc | tgtgacattc | ctcagtgttc | agaagttgaa | 1440 |
| tgcatgacct | gcaatgggga | gagttatcga | ggtctcatgg | atcatacaga | atcaggcaag | 1500 |
| atttgtcagc | gctgggatca | tcagacacca | caccggcaca | aattcttgcc | tgaagatat | 1560 |
| cccgacaagg | gctttgatga | taattattgc | cgcaatcccc | atggccagcc | gaggccatgg | 1620 |
| tgctatactc | ttgaccctca | caccgcgtgg | gagtactgtg | caattaaaac | atgcgctgac | 1680 |
| aaagctgacg | acgacgacaa | acaccaccac | caccaccacc | actag | | 1725 |

40

B

<210> 2
 <211> 574
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Magic F-1 recombinant protein obtained combining hairpin loop and
 kringle domains of human HGF and MSP

<400> 2

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Trp | Val | Thr | Lys | Leu | Leu | Pro | Ala | Leu | Leu | Leu | Gln | His | Val | Leu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Leu | His | Leu | Leu | Leu | Leu | Pro | Ile | Ala | Ile | Pro | Tyr | Ala | Glu | Gly | Gln |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Arg | Lys | Arg | Arg | Asn | Thr | Ile | His | Glu | Phe | Lys | Lys | Ser | Ala | Lys | Thr |
| | 35 | | | | | | 40 | | | | | 45 | | | |
| Thr | Leu | Ile | Lys | Ile | Asp | Pro | Ala | Leu | Lys | Ile | Lys | Thr | Lys | Lys | Val |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Asn | Thr | Ala | Asp | Gln | Cys | Ala | Asn | Arg | Cys | Thr | Arg | Asn | Lys | Gly | Leu |
| 65 | | | | | 70 | | | | 75 | | | | | 80 | |
| Pro | Phe | Thr | Cys | Lys | Ala | Phe | Val | Phe | Asp | Lys | Ala | Arg | Lys | Gln | Cys |
| | | | 85 | | | | | | 90 | | | | | 95 | |
| Leu | Trp | Phe | Pro | Phe | Asn | Ser | Met | Ser | Ser | Gly | Val | Lys | Lys | Glu | Phe |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Gly | His | Glu | Phe | Asp | Leu | Tyr | Glu | Asn | Lys | Asp | Tyr | Ile | Arg | Asn | Cys |
| | 115 | | | | | | 120 | | | | | 125 | | | |
| Ile | Ile | Gly | Lys | Gly | Arg | Ser | Tyr | Lys | Gly | Thr | Val | Ser | Ile | Thr | Lys |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Ser | Gly | Ile | Lys | Cys | Gln | Pro | Trp | Ser | Ser | Met | Ile | Pro | His | Glu | His |
| 145 | | | | 150 | | | | | | 155 | | | | 160 | |
| Ser | Tyr | Arg | Gly | Lys | Asp | Leu | Gln | Glu | Asn | Tyr | Cys | Arg | Asn | Pro | Arg |
| | | | 165 | | | | | 170 | | | | | 175 | | |
| Gly | Glu | Glu | Gly | Gly | Pro | Trp | Cys | Phe | Thr | Ser | Asn | Pro | Glu | Val | Arg |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Tyr | Glu | Val | Cys | Asp | Ile | Pro | Gln | Cys | Ser | Glu | Val | Glu | Cys | Met | Thr |
| | 195 | | | | | 200 | | | | | | 205 | | | |
| Cys | Asn | Gly | Glu | Ser | Tyr | Arg | Gly | Leu | Met | Asp | His | Thr | Glu | Ser | Gly |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Lys | Ile | Cys | Gln | Arg | Trp | Asp | His | Gln | Thr | Pro | His | Arg | His | Lys | Phe |
| 225 | | | | 230 | | | | | | 235 | | | | | 240 |

Leu Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg
 245 250 255
 Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr Thr Leu Asp Pro His
 260 265 270
 Thr Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys Ala Asp Lys Ala Ser
 275 280 285
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Leu
 290 295 300
 Glu Gly Gln Arg Lys Arg Arg Asn Thr Ile His Glu Phe Lys Lys Ser
 305 310 315 320
 Ala Lys Thr Thr Leu Ile Lys Ile Asp Pro Ala Leu Lys Ile Lys Thr
 325 330 335
 Lys Lys Val Asn Thr Ala Asp Gln Cys Ala Asn Arg Cys Thr Arg Asn
 340 345 350
 Lys Gly Leu Pro Phe Thr Cys Lys Ala Phe Val Phe Asp Lys Ala Arg
 355 360 365
 Lys Gln Cys Leu Trp Phe Pro Phe Asn Ser Met Ser Ser Gly Val Lys
 370 375 380
 Lys Glu Phe Gly His Glu Phe Asp Leu Tyr Glu Asn Lys Asp Tyr Ile
 385 390 395 400
 Arg Asn Cys Ile Ile Gly Lys Gly Arg Ser Tyr Lys Gly Thr Val Ser
 405 410 415
 Ile Thr Lys Ser Gly Ile Lys Cys Gln Pro Trp Ser Ser Met Ile Pro
 420 425 430
 His Glu His Ser Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr Cys Arg
 435 440 445
 Asn Pro Arg Gly Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser Asn Pro
 450 455 460
 Glu Val Arg Tyr Glu Val Cys Asp Ile Pro Gln Cys Ser Glu Val Glu
 465 470 475 480
 Cys Met Thr Cys Asn Gly Glu Ser Tyr Arg Gly Leu Met Asp His Thr
 485 490 495
 Glu Ser Gly Lys Ile Cys Gln Arg Trp Asp His Gln Thr Pro His Arg
 500 505 510
 His Lys Phe Leu Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn
 515 520 525
 Tyr Cys Arg Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr Thr Leu
 530 535 540

Asp Pro His Thr Arg Trp Glu Tyr Cys Ala Ile Lys Thr Cys Ala Asp
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Lys Ala Asp Asp Asp Asp Lys His His His His His His His
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<210> 3
<211> 1692
<212> DNA
<213> Artificial Sequence

<220>
<223> Metron F-1 DNA coding sequence

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gtgggtgccg ggccttggca ggaggatgtg gcagatgctg aagagtgtgc tggctcgtgt 180
gggcccttaa tggactgccg ggccttccac tacaacgtga gcagccatgg ttgccaaactg 240
ctgccatgga ctcaacactc gcccacacg aggtgctggc gttctgggcg ctgtgacctc 300
ttccagaaga aagactacgt acggacctgc atcatgaaca atgggggttg gtaccggggc 360
accatggcca cgacctggg tggcctgcc tggcaggctt ggagccacaa gttcccgaat 420
gatcacaagt acacgccac tctccggaat ggcctggaag agaacttctg ccgtaaccct 480
gatggcgacc cgggaggtcc ttggtgctac acaacagacc ctgctgtgcg cttccagagc 540
tgcggcacat aatcctgccg ggaggccgcg tgtgtctggt gcaatggcga ggaataccgc 600
ggcgcggtag accgcacgga gtcagggcgc gagtgccagc gctgggatct tcagcacccg 660
caccagcacc ccttcgagcc gggcaagtcc ctccgaccaag gtctggacga caactattgc 720
cggaatcctg acggctccga gcggccatgg tgctacacta cggatccgca gatcgagcga 780
gagttctgtg acctcccccg ctgcgggtcc gaggcacagc cccgcctcga gggcgggtggc 840
ggttctggtg gcggtggctc cggcgggtggc ggttctctag agggacaaaag gaaaagaaga 900
aatacaattc atgaattcaa aaaatcagca aagactaccc taatcaaaat agatccagca 960
ctgaagataa aaacaaaaaa agtgaatact gcagaccaat gtgctaatag atgtactagg 1020
aataaaggac ttccattcac ttgcaaggct tttgtttttg ataaagcaag aaaacaatgc 1080
ctctggttcc ccttcaatag catgtcaagt ggagtgaata aagaatttgg ccatgaattt 1140
gacctctatg aaaacaaaaga ctacattaga aactgcacat ttggtaaagg acgcagctac 1200
aagggaacag tatctatcac taagagtggc atcaaatgtc agccctggag ttccatgata 1260
ccacacgaac acagctatcg gggtaagac ctacaggaaa actactgtcg aaatcctcga 1320
ggggaagaag ggggacctg gtgtttcaca agcaatccag aggtacgcta cgaagtctgt 1380
gacattcctc agtgttcaga agttgaatgc atgacctgca atggggagag ttatcgaggt 1440
ctcatggatc atacagaatc aggcaagatt tgtcagcgct gggatcatca gacaccacac 1500
cggcacaat tcttgccctga aagatatccc gacaagggtt ttgatgataa ttattgccgc 1560
aatcccgatg gccagccgag gccatggtgc tatactcttg accctcacac ccgctgggag 1620
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caccaccact ag 1692

<210> 4
<211> 563
<212> PRT
<213> Artificial Sequence

<220>
<223> Metron F-1 recombinant protein obtained combining hairpin loop and
kringle domains of human HGF and MSP

<400> 4

Met Gly Trp Leu Pro Leu Leu Leu Leu Leu Thr Gln Cys Leu Gly Val
1 5 10 15
Pro Gly Gln Arg Ser Pro Leu Asn Asp Phe Gln Val Leu Arg Gly Thr
20 25 30
Glu Leu Gln His Leu Leu His Ala Val Val Pro Gly Pro Trp Gln Glu
35 40 45
Asp Val Ala Asp Ala Glu Glu Cys Ala Gly Arg Cys Gly Pro Leu Met
50 55 60
Asp Cys Arg Ala Phe His Tyr Asn Val Ser Ser His Gly Cys Gln Leu
65 70 75 80
Leu Pro Trp Thr Gln His Ser Pro His Thr Arg Leu Arg Arg Ser Gly
85 90 95
Arg Cys Asp Leu Phe Gln Lys Lys Asp Tyr Val Arg Thr Cys Ile Met
100 105 110
Asn Asn Gly Val Gly Tyr Arg Gly Thr Met Ala Thr Thr Val Gly Gly
115 120 125
Leu Pro Cys Gln Ala Trp Ser His Lys Phe Pro Asn Asp His Lys Tyr
130 135 140
Thr Pro Thr Leu Arg Asn Gly Leu Glu Glu Asn Phe Cys Arg Asn Pro
145 150 155 160
Asp Gly Asp Pro Gly Gly Pro Trp Cys Tyr Thr Thr Asp Pro Ala Val
165 170 175
Arg Phe Gln Ser Cys Gly Ile Lys Ser Cys Arg Glu Ala Ala Cys Val
180 185 190
Trp Cys Asn Gly Glu Glu Tyr Arg Gly Ala Val Asp Arg Thr Glu Ser
195 200 205
Gly Arg Glu Cys Gln Arg Trp Asp Leu Gln His Pro His Gln His Pro
210 215 220
Phe Glu Pro Gly Lys Phe Leu Asp Gln Gly Leu Asp Asp Asn Tyr Cys
225 230 235 240
Arg Asn Pro Asp Gly Ser Glu Arg Pro Trp Cys Tyr Thr Thr Asp Pro
245 250 255
Gln Ile Glu Arg Glu Phe Cys Asp Leu Pro Arg Cys Gly Ser Glu Ala
260 265 270
Gln Pro Arg Leu Glu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
275 280 285
Gly Gly Gly Ser Leu Glu Gly Gln Arg Lys Arg Arg Asn Thr Ile His

| 290 | 295 | 300 |
|--|-----|-----|
| Glu Phe Lys Lys Ser Ala Lys Thr Thr Leu Ile Lys Ile Asp Pro Ala 305 310 315 320 | | |
| Leu Lys Ile Lys Thr Lys Lys Val Asn Thr Ala Asp Gln Cys Ala Asn 325 330 335 | | |
| Arg Cys Thr Arg Asn Lys Gly Leu Pro Phe Thr Cys Lys Ala Phe Val 340 345 350 | | |
| Phe Asp Lys Ala Arg Lys Gln Cys Leu Trp Phe Pro Phe Asn Ser Met 355 360 365 | | |
| Ser Ser Gly Val Lys Lys Glu Phe Gly His Glu Phe Asp Leu Tyr Glu 370 375 380 | | |
| Asn Lys Asp Tyr Ile Arg Asn Cys Ile Ile Gly Lys Gly Arg Ser Tyr 385 390 395 400 | | |
| Lys Gly Thr Val Ser Ile Thr Lys Ser Gly Ile Lys Cys Gln Pro Trp 405 410 415 | | |
| Ser Ser Met Ile Pro His Glu His Ser Tyr Arg Gly Lys Asp Leu Gln 420 425 430 | | |
| Glu Asn Tyr Cys Arg Asn Pro Arg Gly Glu Glu Gly Gly Pro Trp Cys 435 440 445 | | |
| Phe Thr Ser Asn Pro Glu Val Arg Tyr Glu Val Cys Asp Ile Pro Gln 450 455 460 | | |
| Cys Ser Glu Val Glu Cys Met Thr Cys Asn Gly Glu Ser Tyr Arg Gly 465 470 475 480 | | |
| Leu Met Asp His Thr Glu Ser Gly Lys Ile Cys Gln Arg Trp Asp His 485 490 495 | | |
| Gln Thr Pro His Arg His Lys Phe Leu Pro Glu Arg Tyr Pro Asp Lys 500 505 510 | | |
| Gly Phe Asp Asp Asn Tyr Cys Arg Asn Pro Asp Gly Gln Pro Arg Pro 515 520 525 | | |
| Trp Cys Tyr Thr Leu Asp Pro His Thr Arg Trp Glu Tyr Cys Ala Ile 530 535 540 | | |
| Lys Thr Cys Ala Asp Lys Ala Asp Asp Asp Asp Lys His His His His 545 550 555 560 | | |
| His His His | | |

<210> 5
 <211> 36
 <212> DNA

45

B

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer targeted to human MSP cDNA

<400> 5

cgcgcggaat tccacatgg ggtggctccc actcct

36

<210> 6

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer targeted to human MSP cDNA

<400> 6

cgcgcgctcg aggcggggct gtgcctcgga ccgcga

36

<210> 7

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer targeted to human HGF cDNA

<400> 7

cgcgcgctcta gagggacaaa ggaaaagaag aaatac

36

<210> 8

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer targeted to human HGF cDNA

<400> 8

cgcgcggaagc ttgtcagcg catgttttaa ttgcac

36

<210> 9

<211> 50

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer used to synthesize the Metron Factor-1 linker sequence

<400> 9

tcgagggcgg tggcggttct ggtggcggtg gtcgcggcgg tggcggttct

50

<210> 10
 <211> 50
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotide primer used to synthesize the Metron Factor-1 linker sequence

 <400> 10
 ctagagaacc gccaccgccg gagccaccgc caccagaacc gccaccgccc 50

 <210> 11
 <211> 50
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotide primer used to insert the tag sequence in Metron Factor-1

 <400> 11
 agctgacgac gacgacaaac accaccacca ccaccaccac tagggtcgac 50

 <210> 12
 <211> 50
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotide primer used to insert the tag sequence in Metron Factor-1

 <400> 12
 agctgtcgac cctagtgggtg gtgggtgggtgg tgggtgtttgt cgtcgtcgtc 50

 <210> 13
 <211> 36
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Oligonucleotide primer targeted to human HGF cDNA

 <400> 13
 cgcgcgggat ccgccagccg ctccagcagc accatg 36

 <210> 14
 <211> 36
 <212> DNA
 <213> Artificial Sequence

47

B

<220>

<223> . Oligonucleotide primer targeted to human HGF cDNA

<400> 14

cgcgcggaagc ttgtcagcg catgttttaa ttgcac

36

<210> 15

<211> 52

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer used to synthesize the Magic Factor-1 linker sequence

<400> 15

agcttcgggc ggtggcggtt ctggtggcgg tggctccggc ggtggcggtt ct

52

<210> 16

<211> 52

<212> DNA

<213> Artificial Sequence

<220>

<223> Oligonucleotide primer used to synthesize the Magic Factor-1 linker sequence

<400> 16

ctagagaacc gccaccgcg gagccaccgc caccagaacc gccaccgccc ga

52

<210> 17

<211> 2172

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(2172)

<223>

<400> 17

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Met Trp Val Thr Lys Leu Leu Pro Ala Leu Leu Leu Gln His Val Leu
1 5 10 15

48

ctg cat ctc ctc ctg ctc ccc atc gcc atc ccc tat gca gag gga caa
Leu His Leu Leu Leu Leu Pro Ile Ala Ile Pro Tyr Ala Glu Gly Gln
20 25 30

96

agg aaa aga aga aat aca att cat gaa ttc aaa aaa tca gca aag act
Arg Lys Arg Arg Asn Thr Ile His Glu Phe Lys Lys Ser Ala Lys Thr
35 40 45

144

48

6

| | |
|---|-----|
| acc cta atc aaa ata gat cca gca ctg aag ata aaa acc aaa aaa gtg | 192 |
| Thr Leu Ile Lys Ile Asp Pro Ala Leu Lys Ile Lys Thr Lys Lys Val | |
| 50 55 60 | |
| aat act gca gac caa tgt gct aat aga tgt act agg aat aaa gga ctt | 240 |
| Asn Thr Ala Asp Gln Cys Ala Asn Arg Cys Thr Arg Asn Lys Gly Leu | |
| 65 70 75 80 | |
| cca ttc act tgc aag gct ttt gtt ttt gat aaa gca aga aaa caa tgc | 288 |
| Pro Phe Thr Cys Lys Ala Phe Val Phe Asp Lys Ala Arg Lys Gln Cys | |
| 85 90 95 | |
| ctc tgg ttc ccc ttc aat agc atg tca agt gga gtg aaa aaa gaa ttt | 336 |
| Leu Trp Phe Pro Phe Asn Ser Met Ser Ser Gly Val Lys Lys Glu Phe | |
| 100 105 110 | |
| ggc cat gaa ttt gac ctc tat gaa aac aaa gac tac att aga aac tgc | 384 |
| Gly His Glu Phe Asp Leu Tyr Glu Asn Lys Asp Tyr Ile Arg Asn Cys | |
| 115 120 125 | |
| atc att ggt aaa gga cgc agc tac aag gga aca gta tct atc act aag | 432 |
| Ile Ile Gly Lys Gly Arg Ser Tyr Lys Gly Thr Val Ser Ile Thr Lys | |
| 130 135 140 | |
| agt ggc atc aaa tgt cag ccc tgg agt tcc atg ata cca cac gaa cac | 480 |
| Ser Gly Ile Lys Cys Gln Pro Trp Ser Ser Met Ile Pro His Glu His | |
| 145 150 155 160 | |
| agc tat cgg ggt aaa gac cta cag gaa aac tac tgt cga aat cct cga | 528 |
| Ser Tyr Arg Gly Lys Asp Leu Gln Glu Asn Tyr Cys Arg Asn Pro Arg | |
| 165 170 175 | |
| ggg gaa gaa ggg gga ccc tgg tgt ttc aca agc aat cca gag gta cgc | 576 |
| Gly Glu Glu Gly Gly Pro Trp Cys Phe Thr Ser Asn Pro Glu Val Arg | |
| 180 185 190 | |
| tac gaa gtc tgt gac att cct cag tgt tca gaa gtt gaa tgc atg acc | 624 |
| Tyr Glu Val Cys Asp Ile Pro Gln Cys Ser Glu Val Glu Cys Met Thr | |
| 195 200 205 | |
| tgc aat ggg gag agt tat cga ggt ctc atg gat cat aca gaa tca ggc | 672 |
| Cys Asn Gly Glu Ser Tyr Arg Gly Leu Met Asp His Thr Glu Ser Gly | |
| 210 215 220 | |
| aag att tgt cag cgc tgg gat cat cag aca cca cac cgg cac aaa ttc | 720 |
| Lys Ile Cys Gln Arg Trp Asp His Gln Thr Pro His Arg His Lys Phe | |
| 225 230 235 240 | |
| ttg cct gaa aga tat ccc gac aag ggc ttt gat gat aat tat tgc cgc | 768 |
| Leu Pro Glu Arg Tyr Pro Asp Lys Gly Phe Asp Asp Asn Tyr Cys Arg | |
| 245 250 255 | |
| aat ccc gat ggc cag ccg agg cca tgg tgc tat act ctt gac cct cac | 816 |
| Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys Tyr Thr Leu Asp Pro His | |
| 260 265 270 | |
| acc cgc tgg gag tac tgt gca att aaa aca tgc gct gac aat act atg | 864 |

49

B

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Thr | Arg | Trp | Glu | Tyr | Cys | Ala | Ile | Lys | Thr | Cys | Ala | Asp | Asn | Thr | Met | |
| | | 275 | | | | | 280 | | | | | 285 | | | | |
| aat | gac | act | gat | gtt | cct | ttg | gaa | aca | act | gaa | tgc | atc | caa | ggg | caa | 912 |
| Asn | Asp | Thr | Asp | Val | Pro | Leu | Glu | Thr | Thr | Glu | Cys | Ile | Gln | Gly | Gln | |
| | 290 | | | | | 295 | | | | | 300 | | | | | |
| gga | gaa | ggc | tac | agg | ggc | act | gtc | aat | acc | att | tgg | aat | gga | att | cca | 960 |
| Gly | Glu | Gly | Tyr | Arg | Gly | Thr | Val | Asn | Thr | Ile | Trp | Asn | Gly | Ile | Pro | |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| tgt | cag | cgt | tgg | gat | tct | cag | tat | cct | cac | gag | cat | gac | atg | act | cct | 1008 |
| Cys | Gln | Arg | Trp | Asp | Ser | Gln | Tyr | Pro | His | Glu | His | Asp | Met | Thr | Pro | |
| | | | | 325 | | | | | 330 | | | | | 335 | | |
| gaa | aat | ttc | aag | tgc | aag | gac | cta | cga | gaa | aat | tac | tgc | cga | aat | cca | 1056 |
| Glu | Asn | Phe | Lys | Cys | Lys | Asp | Leu | Arg | Glu | Asn | Tyr | Cys | Arg | Asn | Pro | |
| | | | 340 | | | | | 345 | | | | | 350 | | | |
| gat | ggg | tct | gaa | tca | ccc | tgg | tgt | ttt | acc | act | gat | cca | aac | atc | cga | 1104 |
| Asp | Gly | Ser | Glu | Ser | Pro | Trp | Cys | Phe | Thr | Thr | Asp | Pro | Asn | Ile | Arg | |
| | | 355 | | | | | 360 | | | | | 365 | | | | |
| gtt | ggc | tac | tgc | tcc | caa | att | cca | aac | tgt | gat | atg | tca | cat | gga | caa | 1152 |
| Val | Gly | Tyr | Cys | Ser | Gln | Ile | Pro | Asn | Cys | Asp | Met | Ser | His | Gly | Gln | |
| | 370 | | | | | 375 | | | | | 380 | | | | | |
| gat | tgt | tat | cgt | ggg | aat | ggc | aaa | aat | tat | atg | ggc | aac | tta | tcc | caa | 1200 |
| Asp | Cys | Tyr | Arg | Gly | Asn | Gly | Lys | Asn | Tyr | Met | Gly | Asn | Leu | Ser | Gln | |
| 385 | | | | | 390 | | | | | 395 | | | | | 400 | |
| aca | aga | tct | gga | cta | aca | tgt | tca | atg | tgg | gac | aag | aac | atg | gaa | gac | 1248 |
| Thr | Arg | Ser | Gly | Leu | Thr | Cys | Ser | Met | Trp | Asp | Lys | Asn | Met | Glu | Asp | |
| | | | | 405 | | | | | 410 | | | | | 415 | | |
| tta | cat | cgt | cat | atc | ttc | tgg | gaa | cca | gat | gca | agt | aag | ctg | aat | gag | 1296 |
| Leu | His | Arg | His | Ile | Phe | Trp | Glu | Pro | Asp | Ala | Ser | Lys | Leu | Asn | Glu | |
| | | | 420 | | | | | 425 | | | | | 430 | | | |
| aat | tac | tgc | cga | aat | cca | gat | gat | gat | gct | cat | gga | ccc | tgg | tgc | tac | 1344 |
| Asn | Tyr | Cys | Arg | Asn | Pro | Asp | Asp | Asp | Ala | His | Gly | Pro | Trp | Cys | Tyr | |
| | | 435 | | | | | 440 | | | | | 445 | | | | |
| acg | gga | aat | cca | ctc | att | cct | tgg | gat | tat | tgc | cct | att | tct | cgt | tgt | 1392 |
| Thr | Gly | Asn | Pro | Leu | Ile | Pro | Trp | Asp | Tyr | Cys | Pro | Ile | Ser | Arg | Cys | |
| | 450 | | | | | 455 | | | | | 460 | | | | | |
| gaa | ggg | gat | acc | aca | cct | aca | ata | gtc | aat | tta | gac | cat | ccc | gta | ata | 1440 |
| Glu | Gly | Asp | Thr | Thr | Pro | Thr | Ile | Val | Asn | Leu | Asp | His | Pro | Val | Ile | |
| 465 | | | | | 470 | | | | 475 | | | | | 480 | | |
| tct | tgt | gcc | aaa | acg | aaa | caa | ttg | cga | gtt | gta | aat | ggg | att | cca | aca | 1488 |
| Ser | Cys | Ala | Lys | Thr | Lys | Gln | Leu | Arg | Val | Val | Asn | Gly | Ile | Pro | Thr | |
| | | | | 485 | | | | | 490 | | | | 495 | | | |
| cga | aca | aac | ata | gga | tgg | atg | gtt | agt | ttg | aga | tac | aga | aat | aaa | cat | 1536 |
| Arg | Thr | Asn | Ile | Gly | Trp | Met | Val | Ser | Leu | Arg | Tyr | Arg | Asn | Lys | His | |

| 500 | | | | | | | | | | 505 | | | | | 510 | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|--|--|--|--|
| atc | tgc | gga | gga | tca | ttg | ata | aag | gag | agt | tgg | gtt | ctt | act | gca | cga | 1584 | | | | |
| Ile | Cys | Gly | Gly | Ser | Leu | Ile | Lys | Glu | Ser | Trp | Val | Leu | Thr | Ala | Arg | | | | | |
| | | 515 | | | | | 520 | | | | | 525 | | | | | | | | |
| cag | tgt | ttc | cct | tct | cga | gac | ttg | aaa | gat | tat | gaa | gct | tgg | ctt | gga | 1632 | | | | |
| Gln | Cys | Phe | Pro | Ser | Arg | Asp | Leu | Lys | Asp | Tyr | Glu | Ala | Trp | Leu | Gly | | | | | |
| | | 530 | | | | 535 | | | | | 540 | | | | | | | | | |
| att | cat | gat | gtc | cac | gga | aga | gga | gat | gag | aaa | tgc | aaa | cag | gtt | ctc | 1680 | | | | |
| Ile | His | Asp | Val | His | Gly | Arg | Gly | Asp | Glu | Lys | Cys | Lys | Gln | Val | Leu | | | | | |
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| aat | gtt | tcc | cag | ctg | gta | tat | ggc | cct | gaa | gga | tca | gat | ctg | gtt | tta | 1728 | | | | |
| Asn | Val | Ser | Gln | Leu | Val | Tyr | Gly | Pro | Glu | Gly | Ser | Asp | Leu | Val | Leu | | | | | |
| | | | | 565 | | | | | 570 | | | | | | 575 | | | | | |
| atg | aag | ctt | gcc | agg | cct | gct | gtc | ctg | gat | gat | ttt | gtt | agt | acg | att | 1776 | | | | |
| Met | Lys | Leu | Ala | Arg | Pro | Ala | Val | Leu | Asp | Asp | Phe | Val | Ser | Thr | Ile | | | | | |
| | | | 580 | | | | | 585 | | | | | 590 | | | | | | | |
| gat | tta | cct | aat | tat | gga | tgc | aca | att | cct | gaa | aag | acc | agt | tgc | agt | 1824 | | | | |
| Asp | Leu | Pro | Asn | Tyr | Gly | Cys | Thr | Ile | Pro | Glu | Lys | Thr | Ser | Cys | Ser | | | | | |
| | | 595 | | | | | 600 | | | | | 605 | | | | | | | | |
| gtt | tat | ggc | tgg | ggc | tac | act | gga | ttg | atc | aac | tat | gat | ggc | cta | tta | 1872 | | | | |
| Val | Tyr | Gly | Trp | Gly | Tyr | Thr | Gly | Leu | Ile | Asn | Tyr | Asp | Gly | Leu | Leu | | | | | |
| | 610 | | | | | 615 | | | | | 620 | | | | | | | | | |
| cga | gtg | gca | cat | ctc | tat | ata | atg | gga | aat | gag | aaa | tgc | agc | cag | cat | 1920 | | | | |
| Arg | Val | Ala | His | Leu | Tyr | Ile | Met | Gly | Asn | Glu | Lys | Cys | Ser | Gln | His | | | | | |
| 625 | | | | | 630 | | | | | 635 | | | | | 640 | | | | | |
| cat | cga | ggg | aag | gtg | act | ctg | aat | gag | tct | gaa | ata | tgt | gct | ggg | gct | 1968 | | | | |
| His | Arg | Gly | Lys | Val | Thr | Leu | Asn | Glu | Ser | Glu | Ile | Cys | Ala | Gly | Ala | | | | | |
| | | | | 645 | | | | | 650 | | | | | 655 | | | | | | |
| gaa | aag | att | gga | tca | gga | cca | tgt | gag | ggg | gat | tat | ggt | ggc | cca | ctt | 2016 | | | | |
| Glu | Lys | Ile | Gly | Ser | Gly | Pro | Cys | Glu | Gly | Asp | Tyr | Gly | Gly | Pro | Leu | | | | | |
| | | | 660 | | | | | 665 | | | | | 670 | | | | | | | |
| gtt | tgt | gag | caa | cat | aaa | atg | aga | atg | gtt | ctt | ggt | gtc | att | gtt | cct | 2064 | | | | |
| Val | Cys | Glu | Gln | His | Lys | Met | Arg | Met | Val | Leu | Gly | Val | Ile | Val | Pro | | | | | |
| | | 675 | | | | | 680 | | | | | 685 | | | | | | | | |
| ggt | cgt | gga | tgt | gcc | att | cca | aat | cgt | cct | ggt | att | ttt | gtc | cga | gta | 2112 | | | | |
| Gly | Arg | Gly | Cys | Ala | Ile | Pro | Asn | Arg | Pro | Gly | Ile | Phe | Val | Arg | Val | | | | | |
| | | 690 | | | | | 695 | | | | 700 | | | | | | | | | |
| gca | tat | tat | gca | aaa | tgg | ata | cac | aaa | att | att | tta | aca | tat | aag | gta | 2160 | | | | |
| Ala | Tyr | Tyr | Ala | Lys | Trp | Ile | His | Lys | Ile | Ile | Leu | Thr | Tyr | Lys | Val | | | | | |
| 705 | | | | | 710 | | | | | 715 | | | | | 720 | | | | | |
| cca | cag | tca | tag | | | | | | | | | | | | | 2172 | | | | |
| Pro | Gln | Ser | | | | | | | | | | | | | | | | | | |

51

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| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Leu | His | Leu | Leu | Leu | Leu | Pro | Ile | Ala | Ile | Pro | Tyr | Ala | Glu | Gly | Gln |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Arg | Lys | Arg | Arg | Asn | Thr | Ile | His | Glu | Phe | Lys | Lys | Ser | Ala | Lys | Thr |
| | | | 35 | | | | 40 | | | | | 45 | | | |
| Thr | Leu | Ile | Lys | Ile | Asp | Pro | Ala | Leu | Lys | Ile | Lys | Thr | Lys | Lys | Val |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Asn | Thr | Ala | Asp | Gln | Cys | Ala | Asn | Arg | Cys | Thr | Arg | Asn | Lys | Gly | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Pro | Phe | Thr | Cys | Lys | Ala | Phe | Val | Phe | Asp | Lys | Ala | Arg | Lys | Gln | Cys |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Leu | Trp | Phe | Pro | Phe | Asn | Ser | Met | Ser | Ser | Gly | Val | Lys | Lys | Glu | Phe |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Gly | His | Glu | Phe | Asp | Leu | Tyr | Glu | Asn | Lys | Asp | Tyr | Ile | Arg | Asn | Cys |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Ile | Ile | Gly | Lys | Gly | Arg | Ser | Tyr | Lys | Gly | Thr | Val | Ser | Ile | Thr | Lys |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Ser | Gly | Ile | Lys | Cys | Gln | Pro | Trp | Ser | Ser | Met | Ile | Pro | His | Glu | His |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Ser | Tyr | Arg | Gly | Lys | Asp | Leu | Gln | Glu | Asn | Tyr | Cys | Arg | Asn | Pro | Arg |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Gly | Glu | Glu | Gly | Gly | Pro | Trp | Cys | Phe | Thr | Ser | Asn | Pro | Glu | Val | Arg |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Tyr | Glu | Val | Cys | Asp | Ile | Pro | Gln | Cys | Ser | Glu | Val | Glu | Cys | Met | Thr |
| | 195 | | | | | 200 | | | | | | 205 | | | |
| Cys | Asn | Gly | Glu | Ser | Tyr | Arg | Gly | Leu | Met | Asp | His | Thr | Glu | Ser | Gly |
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| Lys | Ile | Cys | Gln | Arg | Trp | Asp | His | Gln | Thr | Pro | His | Arg | His | Lys | Phe |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Leu | Pro | Glu | Arg | Tyr | Pro | Asp | Lys | Gly | Phe | Asp | Asp | Asn | Tyr | Cys | Arg |
| | | | | 245 | | | | | 250 | | | | | 255 | |

| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Pro | Asp | Gly | Gln | Pro | Arg | Pro | Trp | Cys | Tyr | Thr | Leu | Asp | Pro | His | 260 | 265 | 270 |
| Thr | Arg | Trp | Glu | Tyr | Cys | Ala | Ile | Lys | Thr | Cys | Ala | Asp | Asn | Thr | Met | 275 | 280 | 285 |
| Asn | Asp | Thr | Asp | Val | Pro | Leu | Glu | Thr | Thr | Glu | Cys | Ile | Gln | Gly | Gln | 290 | 295 | 300 |
| Gly | Glu | Gly | Tyr | Arg | Gly | Thr | Val | Asn | Thr | Ile | Trp | Asn | Gly | Ile | Pro | 305 | 310 | 315 |
| Cys | Gln | Arg | Trp | Asp | Ser | Gln | Tyr | Pro | His | Glu | His | Asp | Met | Thr | Pro | 325 | 330 | 335 |
| Glu | Asn | Phe | Lys | Cys | Lys | Asp | Leu | Arg | Glu | Asn | Tyr | Cys | Arg | Asn | Pro | 340 | 345 | 350 |
| Asp | Gly | Ser | Glu | Ser | Pro | Trp | Cys | Phe | Thr | Thr | Asp | Pro | Asn | Ile | Arg | 355 | 360 | 365 |
| Val | Gly | Tyr | Cys | Ser | Gln | Ile | Pro | Asn | Cys | Asp | Met | Ser | His | Gly | Gln | 370 | 375 | 380 |
| Asp | Cys | Tyr | Arg | Gly | Asn | Gly | Lys | Asn | Tyr | Met | Gly | Asn | Leu | Ser | Gln | 385 | 390 | 395 |
| Thr | Arg | Ser | Gly | Leu | Thr | Cys | Ser | Met | Trp | Asp | Lys | Asn | Met | Glu | Asp | 405 | 410 | 415 |
| Leu | His | Arg | His | Ile | Phe | Trp | Glu | Pro | Asp | Ala | Ser | Lys | Leu | Asn | Glu | 420 | 425 | 430 |
| Asn | Tyr | Cys | Arg | Asn | Pro | Asp | Asp | Asp | Ala | His | Gly | Pro | Trp | Cys | Tyr | 435 | 440 | 445 |
| Thr | Gly | Asn | Pro | Leu | Ile | Pro | Trp | Asp | Tyr | Cys | Pro | Ile | Ser | Arg | Cys | 450 | 455 | 460 |
| Glu | Gly | Asp | Thr | Thr | Pro | Thr | Ile | Val | Asn | Leu | Asp | His | Pro | Val | Ile | 465 | 470 | 475 |
| Ser | Cys | Ala | Lys | Thr | Lys | Gln | Leu | Arg | Val | Val | Asn | Gly | Ile | Pro | Thr | 485 | 490 | 495 |
| Arg | Thr | Asn | Ile | Gly | Trp | Met | Val | Ser | Leu | Arg | Tyr | Arg | Asn | Lys | His | 500 | 505 | 510 |
| Ile | Cys | Gly | Gly | Ser | Leu | Ile | Lys | Glu | Ser | Trp | Val | Leu | Thr | Ala | Arg | 515 | 520 | 525 |
| Gln | Cys | Phe | Pro | Ser | Arg | Asp | Leu | Lys | Asp | Tyr | Glu | Ala | Trp | Leu | Gly | 530 | 535 | 540 |
| Ile | His | Asp | Val | His | Gly | Arg | Gly | Asp | Glu | Lys | Cys | Lys | Gln | Val | Leu | 545 | 550 | 555 |

Asn Val Ser Gln Leu Val Tyr Gly Pro Glu Gly Ser Asp Leu Val Leu
 565 570 575
 Met Lys Leu Ala Arg Pro Ala Val Leu Asp Asp Phe Val Ser Thr Ile
 580 585 590
 Asp Leu Pro Asn Tyr Gly Cys Thr Ile Pro Glu Lys Thr Ser Cys Ser
 595 600 605
 Val Tyr Gly Trp Gly Tyr Thr Gly Leu Ile Asn Tyr Asp Gly Leu Leu
 610 615 620
 Arg Val Ala His Leu Tyr Ile Met Gly Asn Glu Lys Cys Ser Gln His
 625 630 635 640
 His Arg Gly Lys Val Thr Leu Asn Glu Ser Glu Ile Cys Ala Gly Ala
 645 650 655
 Glu Lys Ile Gly Ser Gly Pro Cys Glu Gly Asp Tyr Gly Gly Pro Leu
 660 665 670
 Val Cys Glu Gln His Lys Met Arg Met Val Leu Gly Val Ile Val Pro
 675 680 685
 Gly Arg Gly Cys Ala Ile Pro Asn Arg Pro Gly Ile Phe Val Arg Val
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 cct ggg cag cgc tcg cca ttg aat gac ttc caa gtg ctc cgg ggc aca 96
 Pro Gly Gln Arg Ser Pro Leu Asn Asp Phe Gln Val Leu Arg Gly Thr
 20 25 30
 gag cta cag cac ctg cta cat gcg gtg gtg ccc ggg cct tgg cag gag 144
 Glu Leu Gln His Leu Leu His Ala Val Val Pro Gly Pro Trp Gln Glu
 35 40 45

54

B

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| gat | gtg | gca | gat | gct | gaa | gag | tgt | gct | ggg | cgc | tgt | ggg | ccc | tta | atg | 192 |
| Asp | Val | Ala | Asp | Ala | Glu | Glu | Cys | Ala | Gly | Arg | Cys | Gly | Pro | Leu | Met | |
| | 50 | | | | | 55 | | | | | 60 | | | | | |
| gac | tgc | cgg | gcc | ttc | cac | tac | aac | gtg | agc | agc | cat | ggg | tgc | caa | ctg | 240 |
| Asp | Cys | Arg | Ala | Phe | His | Tyr | Asn | Val | Ser | Ser | His | Gly | Cys | Gln | Leu | |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| ctg | cca | tgg | act | caa | cac | tcg | ccc | cac | acg | agg | ctg | cgg | cgt | tct | ggg | 288 |
| Leu | Pro | Trp | Thr | Gln | His | Ser | Pro | His | Thr | Arg | Leu | Arg | Arg | Ser | Gly | |
| | | | | 85 | | | | | 90 | | | | | 95 | | |
| cgc | tgt | gac | ctc | ttc | cag | aag | aaa | gac | tac | gta | cgg | acc | tgc | atc | atg | 336 |
| Arg | Cys | Asp | Leu | Phe | Gln | Lys | Lys | Asp | Tyr | Val | Arg | Thr | Cys | Ile | Met | |
| | | | 100 | | | | | 105 | | | | | 110 | | | |
| aac | aat | ggg | gtt | ggg | tac | cgg | ggc | acc | atg | gcc | acg | acc | gtg | ggg | ggc | 384 |
| Asn | Asn | Gly | Val | Gly | Tyr | Arg | Gly | Thr | Met | Ala | Thr | Thr | Val | Gly | Gly | |
| | | 115 | | | | | 120 | | | | | 125 | | | | |
| ctg | ccc | tgc | cag | gct | tgg | agc | cac | aag | ttc | ccg | aat | gat | cac | aag | tac | 432 |
| Leu | Pro | Cys | Gln | Ala | Trp | Ser | His | Lys | Phe | Pro | Asn | Asp | His | Lys | Tyr | |
| | 130 | | | | | 135 | | | | | 140 | | | | | |
| acg | ccc | act | ctc | cgg | aat | ggc | ctg | gaa | gag | aac | ttc | tgc | cgt | aac | cct | 480 |
| Thr | Pro | Thr | Leu | Arg | Asn | Gly | Leu | Glu | Glu | Asn | Phe | Cys | Arg | Asn | Pro | |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| gat | ggc | gac | ccc | gga | ggg | cct | tgg | tgc | tac | aca | aca | gac | cct | gct | gtg | 528 |
| Asp | Gly | Asp | Pro | Gly | Gly | Pro | Trp | Cys | Tyr | Thr | Thr | Asp | Pro | Ala | Val | |
| | | | | 165 | | | | | 170 | | | | | 175 | | |
| cgc | ttc | cag | agc | tgc | ggc | atc | aaa | tcc | tgc | cgg | gag | gcc | gcg | tgt | gtc | 576 |
| Arg | Phe | Gln | Ser | Cys | Gly | Ile | Lys | Ser | Cys | Arg | Glu | Ala | Ala | Cys | Val | |
| | | | 180 | | | | | 185 | | | | | 190 | | | |
| tgg | tgc | aat | ggc | gag | gaa | tac | cgc | ggc | gcg | gta | gac | cgc | acg | gag | tca | 624 |
| Trp | Cys | Asn | Gly | Glu | Glu | Tyr | Arg | Gly | Ala | Val | Asp | Arg | Thr | Glu | Ser | |
| | | 195 | | | | | 200 | | | | | 205 | | | | |
| ggg | cgc | gag | tgc | cag | cgc | tgg | gat | ctt | cag | cac | ccg | cac | cag | cac | ccc | 672 |
| Gly | Arg | Glu | Cys | Gln | Arg | Trp | Asp | Leu | Gln | His | Pro | His | Gln | His | Pro | |
| | 210 | | | | | 215 | | | | | 220 | | | | | |
| ttc | gag | ccg | ggc | aag | ttc | ctc | gac | caa | ggg | ctg | gac | gac | aac | tat | tgc | 720 |
| Phe | Glu | Pro | Gly | Lys | Phe | Leu | Asp | Gln | Gly | Leu | Asp | Asp | Asn | Tyr | Cys | |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| cgg | aat | cct | gac | ggc | tcc | gag | cgg | cca | tgg | tgc | tac | act | acg | gat | ccg | 768 |
| Arg | Asn | Pro | Asp | Gly | Ser | Glu | Arg | Pro | Trp | Cys | Tyr | Thr | Thr | Asp | Pro | |
| | | | | 245 | | | | | 250 | | | | | 255 | | |
| cag | atc | gag | cga | gag | ttc | tgt | gac | ctc | ccc | cgc | tgc | ggg | tcc | gag | gca | 816 |
| Gln | Ile | Glu | Arg | Glu | Phe | Cys | Asp | Leu | Pro | Arg | Cys | Gly | Ser | Glu | Ala | |
| | | | 260 | | | | | 265 | | | | | 270 | | | |

| | |
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| cag ccc cgc caa gag gcc aca act gtc agc tgc ttc cgc ggg aag ggt Gln Pro Arg Gln Glu Ala Thr Thr Val Ser Cys Phe Arg Gly Lys Gly 275 280 285 | 864 |
| gag ggc tac cgg ggc aca gcc aat acc acc act gcg ggc gta cct tgc Glu Gly Tyr Arg Gly Thr Ala Asn Thr Thr Thr Ala Gly Val Pro Cys 290 295 300 | 912 |
| cag cgt tgg gac gcg caa atc ccg cat cag cac cga ttt acg cca gaa Gln Arg Trp Asp Ala Gln Ile Pro His Gln His Arg Phe Thr Pro Glu 305 310 315 320 | 960 |
| aaa tac gcg tgc aaa gac ctt cgg gag aac ttc tgc cgg aac ccc gac Lys Tyr Ala Cys Lys Asp Leu Arg Glu Asn Phe Cys Arg Asn Pro Asp 325 330 335 | 1008 |
| ggc tca gag gcg ccc tgg tgc ttc aca ctg cgg ccc ggc atg cgc gcg Gly Ser Glu Ala Pro Trp Cys Phe Thr Leu Arg Pro Gly Met Arg Ala 340 345 350 | 1056 |
| gcc ttt tgc tac cag atc cgg cgt tgt aca gac gac gtg cgg ccc cag Ala Phe Cys Tyr Gln Ile Arg Arg Cys Thr Asp Asp Val Arg Pro Gln 355 360 365 | 1104 |
| gac tgc tac cac ggc gca ggg gag cag tac cgc ggc acg gtc agc aag Asp Cys Tyr His Gly Ala Gly Glu Gln Tyr Arg Gly Thr Val Ser Lys 370 375 380 | 1152 |
| acc cgc aag ggt gtc cag tgc cag cgc tgg tcc gct gag acg ccg cac Thr Arg Lys Gly Val Gln Cys Gln Arg Trp Ser Ala Glu Thr Pro His 385 390 395 400 | 1200 |
| aag ccg cag ttc acg ttt acc tcc gaa ccg cat gca caa ctg gag gag Lys Pro Gln Phe Thr Phe Thr Ser Glu Pro His Ala Gln Leu Glu Glu 405 410 415 | 1248 |
| aac ttc tgc cgg aac cca gat ggg gat agc cat ggg ccc tgg tgc tac Asn Phe Cys Arg Asn Pro Asp Gly Asp Ser His Gly Pro Trp Cys Tyr 420 425 430 | 1296 |
| acg atg gac cca agg acc cca ttc gac tac tgt gcc ctg cga cgc tgc Thr Met Asp Pro Arg Thr Pro Phe Asp Tyr Cys Ala Leu Arg Arg Cys 435 440 445 | 1344 |
| gct gat gac cag ccg cca tca atc ctg gac ccc cca gac cag gtg cag Ala Asp Asp Gln Pro Pro Ser Ile Leu Asp Pro Pro Asp Gln Val Gln 450 455 460 | 1392 |
| ttt gag aag tgt ggc aag agg gtg gat cgg ctg gat cag cgg cgt tcc Phe Glu Lys Cys Gly Lys Arg Val Asp Arg Leu Asp Gln Arg Arg Ser 465 470 475 480 | 1440 |
| aag ctg cgc gtg gtt ggg ggc cat ccg ggc aac tca ccc tgg aca gtc Lys Leu Arg Val Val Gly Gly His Pro Gly Asn Ser Pro Trp Thr Val 485 490 495 | 1488 |
| agc ttg cgg aat cgg cag ggc cag cat ttc tgc ggg ggg tct cta gtg | 1536 |

56

B

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Ser | Leu | Arg | Asn | Arg | Gln | Gly | Gln | His | Phe | Cys | Gly | Gly | Ser | Leu | Val | |
| | | | 500 | | | | | 505 | | | | | | 510 | | |
| aag | gag | cag | tgg | ata | ctg | act | gcc | cgg | cag | tgc | ttc | tcc | tcc | tgc | cat | 1584 |
| Lys | Glu | Gln | Trp | Ile | Leu | Thr | Ala | Arg | Gln | Cys | Phe | Ser | Ser | Cys | His | |
| | | 515 | | | | | 520 | | | | | 525 | | | | |
| atg | cct | ctc | acg | ggc | tat | gag | gta | tgg | ttg | ggc | acc | ctg | ttc | cag | aac | 1632 |
| Met | Pro | Leu | Thr | Gly | Tyr | Glu | Val | Trp | Leu | Gly | Thr | Leu | Phe | Gln | Asn | |
| | 530 | | | | | 535 | | | | | 540 | | | | | |
| cca | cag | cat | gga | gag | cca | agc | cta | cag | cgg | gtc | cca | gta | gcc | aag | atg | 1680 |
| Pro | Gln | His | Gly | Glu | Pro | Ser | Leu | Gln | Arg | Val | Pro | Val | Ala | Lys | Met | |
| 545 | | | | | 550 | | | | | 555 | | | | | 560 | |
| gtg | tgt | ggg | ccc | tca | ggc | tcc | cag | ctt | gtc | ctg | ctc | aag | ctg | gag | aga | 1728 |
| Val | Cys | Gly | Pro | Ser | Gly | Ser | Gln | Leu | Val | Leu | Leu | Lys | Leu | Glu | Arg | |
| | | | | 565 | | | | | 570 | | | | | | 575 | |
| tct | gtg | acc | ctg | aac | cag | cgt | gtg | gcc | ctg | atc | tgc | ctg | ccc | cct | gaa | 1776 |
| Ser | Val | Thr | Leu | Asn | Gln | Arg | Val | Ala | Leu | Ile | Cys | Leu | Pro | Pro | Glu | |
| | | | 580 | | | | | 585 | | | | | 590 | | | |
| tgg | tat | gtg | gtg | cct | cca | ggg | acc | aag | tgt | gag | att | gca | ggc | tgg | ggt | 1824 |
| Trp | Tyr | Val | Val | Pro | Pro | Gly | Thr | Lys | Cys | Glu | Ile | Ala | Gly | Trp | Gly | |
| | | 595 | | | | | 600 | | | | | 605 | | | | |
| gag | acc | aaa | ggt | acg | ggt | aat | gac | aca | gtc | cta | aat | gtg | gcc | ttt | ctg | 1872 |
| Glu | Thr | Lys | Gly | Thr | Gly | Asn | Asp | Thr | Val | Leu | Asn | Val | Ala | Phe | Leu | |
| | 610 | | | | | 615 | | | | | 620 | | | | | |
| aat | gtt | atc | tcc | aac | cag | gag | tgt | aac | atc | aag | cac | cga | gga | cgt | gtg | 1920 |
| Asn | Val | Ile | Ser | Asn | Gln | Glu | Cys | Asn | Ile | Lys | His | Arg | Gly | Arg | Val | |
| 625 | | | | | 630 | | | | | 635 | | | | | 640 | |
| cgg | gag | agt | gag | atg | tgc | act | gag | gga | ctg | ttg | gcc | cct | gtg | ggg | gcc | 1968 |
| Arg | Glu | Ser | Glu | Met | Cys | Thr | Glu | Gly | Leu | Leu | Ala | Pro | Val | Gly | Ala | |
| | | | | 645 | | | | | 650 | | | | | | 655 | |
| tgt | gag | ggt | gac | tac | ggg | ggc | cca | ctt | gcc | tgc | ttt | acc | cac | aac | tgc | 2016 |
| Cys | Glu | Gly | Asp | Tyr | Gly | Gly | Pro | Leu | Ala | Cys | Phe | Thr | His | Asn | Cys | |
| | | | 660 | | | | | 665 | | | | | 670 | | | |
| tgg | gtc | ctg | gaa | gga | att | ata | atc | ccc | aac | cga | gta | tgc | gca | agg | tcc | 2064 |
| Trp | Val | Leu | Glu | Gly | Ile | Ile | Ile | Pro | Asn | Arg | Val | Cys | Ala | Arg | Ser | |
| | | 675 | | | | | 680 | | | | | 685 | | | | |
| cgc | tgg | cca | gct | gtc | ttc | acg | cgt | gtc | tct | gtg | ttt | gtg | gac | tgg | att | 2112 |
| Arg | Trp | Pro | Ala | Val | Phe | Thr | Arg | Val | Ser | Val | Phe | Val | Asp | Trp | Ile | |
| | 690 | | | | | 695 | | | | | 700 | | | | | |
| cac | aag | gtc | atg | aga | ctg | ggt | tag | | | | | | | | | 2136 |
| His | Lys | Val | Met | Arg | Leu | Gly | | | | | | | | | | |
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57

B

<211> 711
<212> PRT
<213> Homo sapiens

<400> 20

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| Met | Gly | Trp | Leu | Pro | Leu | Leu | Leu | Leu | Leu | Thr | Gln | Cys | Leu | Gly | Val | |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| Pro | Gly | Gln | Arg | Ser | Pro | Leu | Asn | Asp | Phe | Gln | Val | Leu | Arg | Gly | Thr | |
| | | | 20 | | | | | 25 | | | | | 30 | | | |
| Glu | Leu | Gln | His | Leu | Leu | His | Ala | Val | Val | Pro | Gly | Pro | Trp | Gln | Glu | |
| | | 35 | | | | | 40 | | | | | 45 | | | | |
| Asp | Val | Ala | Asp | Ala | Glu | Glu | Cys | Ala | Gly | Arg | Cys | Gly | Pro | Leu | Met | |
| | 50 | | | | | 55 | | | | | 60 | | | | | |
| Asp | Cys | Arg | Ala | Phe | His | Tyr | Asn | Val | Ser | Ser | His | Gly | Cys | Gln | Leu | |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| Leu | Pro | Trp | Thr | Gln | His | Ser | Pro | His | Thr | Arg | Leu | Arg | Arg | Ser | Gly | |
| | | | | 85 | | | | | 90 | | | | | 95 | | |
| Arg | Cys | Asp | Leu | Phe | Gln | Lys | Lys | Asp | Tyr | Val | Arg | Thr | Cys | Ile | Met | |
| | | | 100 | | | | | 105 | | | | | 110 | | | |
| Asn | Asn | Gly | Val | Gly | Tyr | Arg | Gly | Thr | Met | Ala | Thr | Thr | Val | Gly | Gly | |
| | | 115 | | | | | 120 | | | | | 125 | | | | |
| Leu | Pro | Cys | Gln | Ala | Trp | Ser | His | Lys | Phe | Pro | Asn | Asp | His | Lys | Tyr | |
| | 130 | | | | | 135 | | | | | 140 | | | | | |
| Thr | Pro | Thr | Leu | Arg | Asn | Gly | Leu | Glu | Glu | Asn | Phe | Cys | Arg | Asn | Pro | |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| Asp | Gly | Asp | Pro | Gly | Gly | Pro | Trp | Cys | Tyr | Thr | Thr | Asp | Pro | Ala | Val | |
| | | | | 165 | | | | | 170 | | | | | 175 | | |
| Arg | Phe | Gln | Ser | Cys | Gly | Ile | Lys | Ser | Cys | Arg | Glu | Ala | Ala | Cys | Val | |
| | | | 180 | | | | | 185 | | | | | 190 | | | |
| Trp | Cys | Asn | Gly | Glu | Glu | Tyr | Arg | Gly | Ala | Val | Asp | Arg | Thr | Glu | Ser | |
| | 195 | | | | | | 200 | | | | | 205 | | | | |
| Gly | Arg | Glu | Cys | Gln | Arg | Trp | Asp | Leu | Gln | His | Pro | His | Gln | His | Pro | |
| | 210 | | | | | 215 | | | | | 220 | | | | | |
| Phe | Glu | Pro | Gly | Lys | Phe | Leu | Asp | Gln | Gly | Leu | Asp | Asp | Asn | Tyr | Cys | |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| Arg | Asn | Pro | Asp | Gly | Ser | Glu | Arg | Pro | Trp | Cys | Tyr | Thr | Thr | Asp | Pro | |
| | | | | 245 | | | | | 250 | | | | | 255 | | |
| Gln | Ile | Glu | Arg | Glu | Phe | Cys | Asp | Leu | Pro | Arg | Cys | Gly | Ser | Glu | Ala | |
| | | | 260 | | | | | 265 | | | | | 270 | | | |

58

11B

Gln Pro Arg Gln Glu Ala Thr Thr Val Ser Cys Phe Arg Gly Lys Gly
 275 280 285
 Glu Gly Tyr Arg Gly Thr Ala Asn Thr Thr Thr Ala Gly Val Pro Cys
 290 295 300
 Gln Arg Trp Asp Ala Gln Ile Pro His Gln His Arg Phe Thr Pro Glu
 305 310 315 320
 Lys Tyr Ala Cys Lys Asp Leu Arg Glu Asn Phe Cys Arg Asn Pro Asp
 325 330 335
 Gly Ser Glu Ala Pro Trp Cys Phe Thr Leu Arg Pro Gly Met Arg Ala
 340 345 350
 Ala Phe Cys Tyr Gln Ile Arg Arg Cys Thr Asp Asp Val Arg Pro Gln
 355 360 365
 Asp Cys Tyr His Gly Ala Gly Glu Gln Tyr Arg Gly Thr Val Ser Lys
 370 375 380
 Thr Arg Lys Gly Val Gln Cys Gln Arg Trp Ser Ala Glu Thr Pro His
 385 390 395 400
 Lys Pro Gln Phe Thr Phe Thr Ser Glu Pro His Ala Gln Leu Glu Glu
 405 410 415
 Asn Phe Cys Arg Asn Pro Asp Gly Asp Ser His Gly Pro Trp Cys Tyr
 420 425 430
 Thr Met Asp Pro Arg Thr Pro Phe Asp Tyr Cys Ala Leu Arg Arg Cys
 435 440 445
 Ala Asp Asp Gln Pro Pro Ser Ile Leu Asp Pro Pro Asp Gln Val Gln
 450 455 460
 Phe Glu Lys Cys Gly Lys Arg Val Asp Arg Leu Asp Gln Arg Arg Ser
 465 470 475 480
 Lys Leu Arg Val Val Gly Gly His Pro Gly Asn Ser Pro Trp Thr Val
 485 490 495
 Ser Leu Arg Asn Arg Gln Gly Gln His Phe Cys Gly Gly Ser Leu Val
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 Lys Glu Gln Trp Ile Leu Thr Ala Arg Gln Cys Phe Ser Ser Cys His
 515 520 525
 Met Pro Leu Thr Gly Tyr Glu Val Trp Leu Gly Thr Leu Phe Gln Asn
 530 535 540
 Pro Gln His Gly Glu Pro Ser Leu Gln Arg Val Pro Val Ala Lys Met
 545 550 555 560
 Val Cys Gly Pro Ser Gly Ser Gln Leu Val Leu Leu Lys Leu Glu Arg
 565 570 575

59

B

Ser Val Thr Leu Asn Gln Arg Val Ala Leu Ile Cys Leu Pro Pro Glu
580 585 590

Trp Tyr Val Val Pro Pro Gly Thr Lys Cys Glu Ile Ala Gly Trp Gly
595 600 605

Glu Thr Lys Gly Thr Gly Asn Asp Thr Val Leu Asn Val Ala Phe Leu
610 615 620

Asn Val Ile Ser Asn Gln Glu Cys Asn Ile Lys His Arg Gly Arg Val
625 630 635 640

Arg Glu Ser Glu Met Cys Thr Glu Gly Leu Leu Ala Pro Val Gly Ala
645 650 655

Cys Glu Gly Asp Tyr Gly Gly Pro Leu Ala Cys Phe Thr His Asn Cys
660 665 670

Trp Val Leu Glu Gly Ile Ile Ile Pro Asn Arg Val Cys Ala Arg Ser
675 680 685

Arg Trp Pro Ala Val Phe Thr Arg Val Ser Val Phe Val Asp Trp Ile
690 695 700

His Lys Val Met Arg Leu Gly
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gctacatgcg gtgggtgcccg ggccttggca ggaggatgtg gcagatgctg aagagtgtgc 180
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ttgccaaactg ctgccatgga ctcaacactc gccccacacg aggtctgcggc gttctgggcg 300
ctgtgacctc ttccagaaga aagactacgt acggacctgc atcatgaaca atgggggttg 360
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gttcccgaat gatcacaagt acacgcccac tctccggaat ggcttgggaag agaacttctg 480
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ccatgaattt gacctctatg aaaacaaaga ctacattaga aactgcatca ttggtaaagg 1200

60

B

| | | | | | | |
|------------|------------|-------------|------------|------------|------------|------|
| acgcagctac | aagggaacag | tatctatcac | taagagtggc | atcaaagtgc | agccctggag | 1260 |
| ttccatgata | ccacacgaac | acagctatcg | gggtaaagac | ctacaggaaa | actactgtcg | 1320 |
| aaatcctcga | ggggaagaag | ggggaccctg | gtgtttcaca | agcaatccag | aggtagccta | 1380 |
| cgaagtctgt | gacattcctc | agtgttcaga | agttgaatgc | atgacctgca | atggggagag | 1440 |
| ttatcgaggt | ctcatggatc | atacagaatc | aggcaagatt | tgtcagcgct | gggatcatca | 1500 |
| gacaccacac | cggcacaaat | tcttgccctga | aagatatccc | gacaagggct | ttgatgataa | 1560 |
| ttattgccgc | aatcccgatg | gccagccgag | gccatggtgc | tatactcttg | accctcacac | 1620 |
| ccgctgggag | tactgtgcaa | ttaaaacatg | cgctgacaaa | gctgacgacg | acgacaaaca | 1680 |
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<210> 22
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| ctgcagcatg | tcctcctgca | tctcctcctg | ctccccatcg | ccatccccta | tgcagaggga | 120 |
| caaaggaaaa | gaagaaatac | aattcatgaa | ttcaaaaaat | cagcaaagac | taccctaatac | 180 |
| aaaatagatc | cagcactgaa | gataaaaacc | aaaaaagtga | atactgcaga | ccaatgtgct | 240 |
| aatagatgta | ctaggaataa | aggacttcca | ttcacttgca | aggcttttgt | ttttgataaa | 300 |
| gcaagaaaac | aatgcctctg | gttccccttc | aatagcatgt | caagtggagt | gaaaaaagaa | 360 |
| tttggccatg | aatttgacct | ctatgaaaac | aaagactaca | ttagaaactg | catcattggt | 420 |
| aaaggacgca | gctacaaggg | aacagtatct | atcactaaga | gtggcatcaa | atgtcagccc | 480 |
| tggagtcca | tgataccaca | cgaacacagc | tatcggggta | aagacctaca | ggaaaactac | 540 |
| tgtcgaaatc | ctcgagggga | agaaggggga | ccctggtggt | tcacaagcaa | tccagaggta | 600 |
| cgctacgaag | tctgtgacat | tcctcagtgt | tcagaagttg | aatgcatgac | ctgcaatggg | 660 |
| gagagttatc | gaggtctcat | ggatcataca | gaatcaggca | agattttgtca | gcgctgggat | 720 |
| catcagacac | cacaccggca | caaattcttg | cctgaaagat | atcccgacaa | gggctttgat | 780 |
| gataattatt | gccgcaatcc | cgatggccag | ccgaggccat | ggtgctatac | tcttgaccct | 840 |
| cacaccgcgt | gggagtactg | tgcaattaaa | acatgcgctg | acaaagcttc | gggcggtggc | 900 |
| ggttctggtg | gcggtggctc | cggcggtggc | ggttctctag | agggacaaag | gaaaagaaga | 960 |
| aatacaattc | atgaattcaa | aaaatcagca | aagactaccc | taatcaaaat | agatccagca | 1020 |
| ctgaagataa | aaaccacaaa | agtgaatact | gcagaccaat | gtgctaatag | atgtactagg | 1080 |
| aataaaggac | ttccattcac | ttgcaaggct | tttgtttttg | ataaagcaag | aaaacaatgc | 1140 |
| ctctggttcc | ccttcaatag | catgtcaagt | ggagtgaaaa | aagaatttgg | ccatgaattt | 1200 |
| gacctctatg | aaaacaaaga | ctacattaga | aactgcatca | ttggtaaagg | acgcagctac | 1260 |
| aagggaacag | tatctatcac | taagagtggc | atcaaagtgc | agccctggag | ttccatgata | 1320 |
| ccacacgaac | acagctatcg | gggtaaagac | ctacaggaaa | actactgtcg | aaatcctcga | 1380 |
| ggggaagaag | ggggaccctg | gtgtttcaca | agcaatccag | aggtagccta | cgaagtctgt | 1440 |
| gacattcctc | agtgttcaga | agttgaatgc | atgacctgca | atggggagag | ttatcgaggt | 1500 |
| ctcatggatc | atacagaatc | aggcaagatt | tgtcagcgct | gggatcatca | gacaccacac | 1560 |
| cggcacaaat | tcttgccctga | aagatatccc | gacaagggct | ttgatgataa | ttattgccgc | 1620 |
| aatcccgatg | gccagccgag | gccatggtgc | tatactcttg | accctcacac | ccgctgggag | 1680 |
| tactgtgcaa | ttaaaacatg | cgctgacaaa | gctgacgacg | acgacaaaca | ccaccaccac | 1740 |
| caccaccact | agggtcgac | | | | | 1759 |

61

B